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# Prediction of *In Vivo* Performance of Dabigatran Capsules Marketed in Nepal from *In Vitro* (Dissolution) Data Using Numerical Convolution Method

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## Abstract

Dabigatran is an oral prodrug used for the prevention of venous thromboembolic events or stroke; a life-saving drug. The aim of present study was to ensure the *in vivo* performance of the dabigatran capsules marketed in Nepal. The study predicts *in vivo* study data of locally produced Dabigatran capsules (coded as Product A and Product B which are marketed without *in vivo* performance study using *In Vitro In Vivo* correlation (IVIVC) method. From predicted plasma drug concentration-time data, the Area Under the Curve (AUC), and maximum plasma drug concentration (Cmax) were determined for both test products A and B using numerical convolution technique. The analytical method used in this research is developed by National Medicine Laboratories. Acetonitrile and triethylamine (5 mL Triethylamine in 1000 mL of water, adjust pH to 3.0 with orthophosphoric acid) is used as mobile phase in chromatographic system. The observed value of Cmax and AUC of the Reference Product was 105.63 ng/mL and 1708.28 ng*h/mL respectively. Similarly, Cmax and AUC of "Product A" from the convolution method was found to be 105.08 ng/mL, 1722.91 ng*h/mL while the Cmax and AUC of "Product B" was found to be 96.83 ng/mL, and 1583.40 ng*h/mL. The percentage prediction error (%PE) values for Cmax and AUC were found to be 0.52% and -0.85% for "Product A" and 9.09% and 7.89% for "Product B" respectively. The predicted error of AUC and Cmax are within the ±20% range for both local generic products (Product A and Product B). The rate and extent of absorption of test products were found to be similar in convolution method.

***Keywords:*** *IVIVC, Dabigatran, Bioequivalence, Convolution*



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## 1. Introduction

Bioavailability or bioequivalence study tells the *in vivo* performance of the products which should be done before coming to market but our regulatory authority provides marketing license without *in vivo* performance data. This is the reason why it is difficult to perform brand substitution in the Nepalese context and because of these reasons prescriptions are written on brand names.

Dabigatran etexilate is a synthetic prodrug with a molecular weight of 628 Da (DBO, n.d.).

Yellow-white or yellow non-hygroscopic crystalline powder, dabigatran etexilate, in the neutral form has the apparent partition coefficient of log P = 3.8, and the dissociation constants of pKa1 = 4.0 0.1 (benzimidazole moiety) and pKa2 = 6.7 0.1. (Carbamic acid hexyl ester moiety). Since solubility is greatly influenced by pH, it increases with acidic pH. The drug's solubility in pure water was determined to be 1.8 mg/mL in a saturated solution. Dabigatran etexilate mesylate is a Class II drug substance according to the Biopharmaceutical Classification System and was chosen for the current inquiry as a model drug owing to its low solubility in water (pH 3 to pH 7.5) and relatively high passive permeability (Solanki *et al.*, 2018; Chai *et al.*, 2016; El-Samaligy *et al.*, 2006; Härtter *et al.*, 2013).

Dabigatran Etexilate, an oral prodrug, is hydrolyzed to yield the direct thrombin inhibitor dabigatran, a competitive and reversible inhibitor. In individuals for whom anticoagulant medication is recommended, dabigatran etexilate may be administered to lower the risk of venous thromboembolic events. Unlike warfarin, which requires lab monitoring because of its unpredictable anticoagulant effects, heparin does not. The FDA authorized dabigatran etexilate in 2010. Multiple dosage forms and brands are allowed to be marketed in Nepal without robust *in vivo* data. Performance of over-the-counter products and those with wide therapeutic margins may not be affected by alteration of different brands, however, for an anticoagulant drug like dabigatran, *in vivo* performance needs to be checked as this drug has a fatal adverse effect like major bleeding in case of altered bioavailability. Efficacy i.e., prevention of thromboembolism is also reduced in the case of low BA. So, the *in vivo* performance of this drug needs to be monitored. Imported multinational products may be tested for *in vivo* performance but locally produced products are not tested for *in vivo* performance in Nepal and are used as brand substitution products.

As Dabigatran is a life-saving drug it's *in vivo* performance assurance is very imperative from the patient's side for two reasons; absence of therapeutic effect would lead to significant waste of money considering the expensive price of the drug while high bioavailability or *in vivo* performance, may result in serious effects (adverse drug reactions) in patients which may be fatal sometimes. Bioavailability and bioequivalence are very expensive and time-consuming. Thus *In Vitro In Vivo* correlation (IVIVC) is used to predict *in vivo* performance of products from *in vitro* (dissolution) data which overcomes the disadvantages of in vivo study for bioequivalence. Dissolution study was carried out for the test product and reference products and their plasma drug concentration was determined using this numerical convolution technique. From plasma drug concentration-time data, the Area under the curve (AUC) and maximum plasma drug concentration (Cmax) was determined for both test and reference products. The extent and rate of drug absorption is indicated by AUC and Cmax respectively.

## 2. Materials and Methods

### *2.1. Methods (NML, n.d.)*

Analytical Profile No.: DAB075/076/AP037

*2.1.1. Identification*

In the assay, the principle peak in the chromatogram obtained with the sample solution should correspond to the peak in the chromatogram obtained with the reference standard solution of Dabigatran Etexilate.

*2.1.2. Dissolution*

Determine by Thin Layer Chromatography

*2.1.3. Dissolution Parameters*

Apparatus: Basket

**Table 1: List of the Chemicals, Apparatus and Equipment Used During the Research Process**

| Chemicals | Apparatus | Equipment with their Company Names |
|---|---|---|
| Acetonitrile (HPLC Grade) | Volumetric Flask (25,50 mL) | HPLC- Shimadzu, Agilent Technologies |
| Triethanolamine | Measuring Cylinder (500, 1000 mL) | Dissolution Tester-Electrolab |
| Orthophosphoric Acid | Pipette (1,2,5 mL) | Analytical Balance-Shimadzu |
| HPLC Water | HPLC vials | pH Meter-Hanna Instruments |
| Dabigatran Standard (Potency-99.04%, LOD-0.38) | Dissolution Sampling Tubes | Sonicator Disintegration Tester |

Medium: 900 mL, 0.01 N HCL

Speed and Time: 100 rpm at 45 min

Time: 45 minutes

Temperature: 37 °C ± 0.5 °C

*2.1.4. Chromatographic System*

Column: C18, (250*4.6 mm), 5 µm

Flow rate: 1.0 mL/min

Wavelength: 341 nm

Injection volume: 10 µL

Column Temp.: 27 °C

Detector: UV

Mobile phase:

Buffer: Acetonitrile (40:60)

Buffer: Take 5 mL Triethylamine in 1000 mL of water, adjust pH to 3.0 with orthophosphoric acid

*2.1.5. Test Solution*

Withdraw a suitable volume of the sample after 45 min. Filter the sample.

*2.1.6. Reference Solution*

Weigh accurately about 48.0 mg Dabigatran Etexilate (as Mesylate) working standard in 50 mL volumetric flask. Add about 30 mL of dissolution medium and sonicate for about 15 min and make up the volume to 50 mL with dissolution medium. Dilute 2 mL of resulting solution to 20 mL with dissolution medium.

*2.1.7. Procedure*

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates. The tailing factor is not more than 2.0 and the relative standard deviation for replicate injections in not more than 2.0%. Inject sample and measure the peak responses. Calculate the % release of the drug.

*2.1.8. Limit*

D. NLT 75 % of the stated amount

## *2.2. Invitro Evaluation of Dabigatran Etexilate Capsule*

*2.2.1. Weight Variation Test*

The weight variation test is done to demonstrate the uniformity of dosage units. The average weight of the capsule was determined from twenty randomly selected capsules. The individual weight of twenty capsules

was taken, and from this percentage deviation of each capsule was determined using the average weight. The deviation of the individual weight of the capsule from the average weight of the capsule should not exceed the limits given below:

1. 20 capsules were selected at random.
2. One capsule was weighed. The capsule was opened and the contents were removed as completely as possible. The empty shells were then weighed. The net weight of its content was determined by subtracting the weight of the shells from the weight of the intact capsule.
3. The procedure was repeated with the other 19 capsules.
4. The average net weight was determined from the sum of the individual net weights.
5. The percentage deviation from the average net weight for each capsule was determined. The deviation of individual net weight should not exceed the limits given below: (PPD, 2015).

$$Percentage\ deviation\ of\ each\ capsule = \frac{Weight\ of\ each\ capsule - Average\ weight\ of\ capsule}{Average\ weight\ of\ capsule} \times 100$$

*2.2.2. Disintegration Test*

The disintegration test is carried out in order to determine whether tablets or capsules will disintegrate within the set time when immersed in liquid medium repetitively.

Disintegration does not imply to complete dissolution of the unit or even of its active constituent for the purpose of this test. Complete disintegration is defined as that state in which any residue of the dosage forms (tablets) in the basket-rack assembly, except fragments of insoluble coating or capsule shell, is a soft mass having no palpably firm core (PPD, 2015).

The apparatus consists of a basket-rack assembly containing six open-ended transparent tubes of USP-specified dimensions, held vertically upon a 10-mesh stainless steel wire screen.

During testing, a tablet is placed in each of the six tubes of the basket, and through the use of a mechanical device, the basket is raised and lowered in a bath of fluid (e.g., water, or as prescribed in the individual drug monograph) at 29 to 32 cycles per minute, the wire screen always below the level of the fluid.

Disintegration time for hard gelatin capsule 30 min

Disintegration time for soft gelatin capsules 60 mins

Factors affecting the disintegration of tablets include: (NML, n.d.)

- Medium used
- The temperature of the test media
- Operator's experience
- Nature of the drug

*2.2.3. Dissolution Test*

This test measures the amount of time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions (Table 2). It is intended to provide a step toward the evaluation of the physiological availability of the drug substances (NML, n.d.).

**Table 2: Pharmacopoeial Limit for Weight Variation of Capsules**

| Average Weight | % Deviation |
|---|---|
| Less than 300 mg | 10 |
| 300 mg or more | 7.5 |

The dissolution test was carried out for the reference product and two test products, and sampling was done at 9 different time points within 45 min of 5 min time difference. The cumulative drug release for all three products was calculated after replenishing 10 mL of the drug product. The amount of drug released within the sampling interval was used to calculate the rate and extent of drug absorption of test products (Figures 1, 2 and 3).

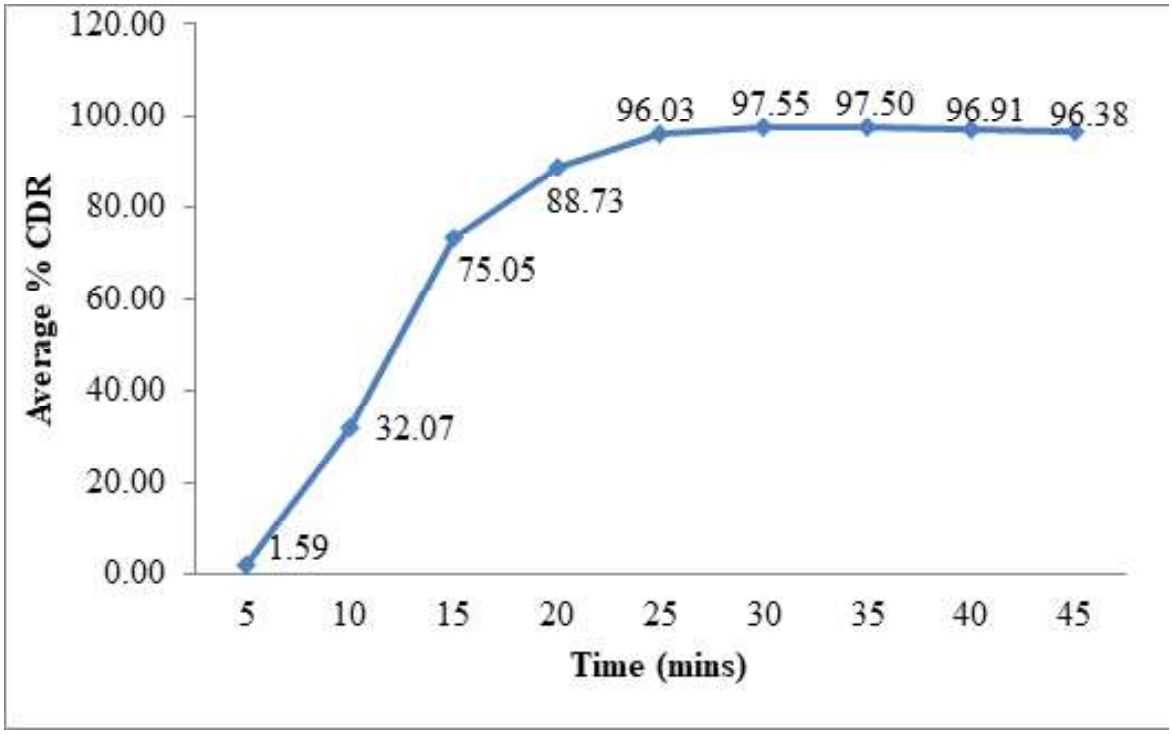


**Figure 1: Average % CDR of Reference Product**

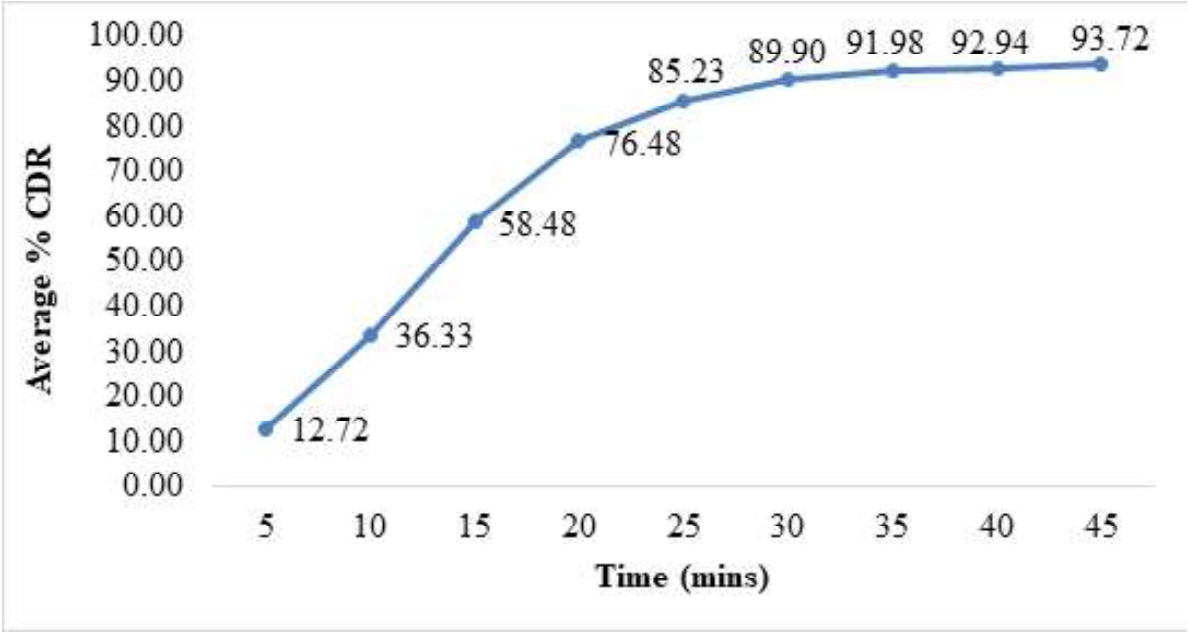


**Figure 2: Average % CDR of Test Product A**

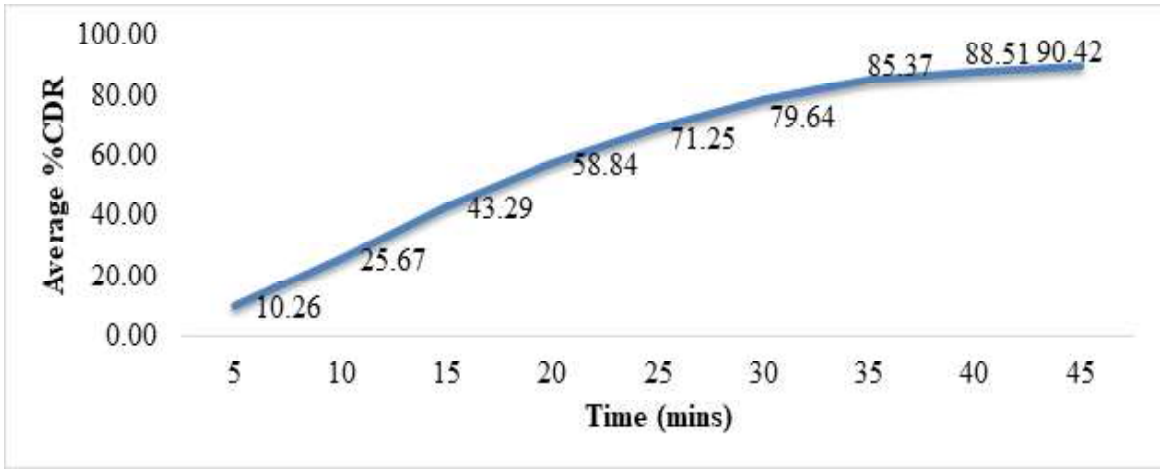


**Figure 3: Average % CDR of Test Product B**

Various factors can affect the dissolution of a drug; they are classified under three categories as follows:

**2.2.3.1. Physiochemical Properties of the Drug**

a) Polymorphic Form: A metastable form of a solid has higher solubility and dissolution compared to its stable counterpart.

b) Particle Size: The smaller the particle size of a solid, the larger the particle surface area and the higher the dissolution.

c) Salt Form: A salt form of a drug has a higher aqueous solubility compared to its conjugate acid or base, as well as higher dissolution.

d) Hydrates versus Anhydrates: The anhydrous form shows higher dissolution than hydrates due to their solubility differences.

**2.2.3.2. Factors Related to Tablet Manufacturing**

a) The amount and type of binder can affect the hardness, disintegration, and dissolution of tablets.

b) The method of granulation, granule size, and size distribution can affect tablet dissolution.

c) The concentration and type of disintegrants used, as well as the method of their addition, can affect disintegration and dissolution.

d) Compression load can influence density, porosity, hardness, disintegration, and dissolution of tablets.

**2.2.3.3. Factors Related to Method of Dissolution Study (NML, n.d.)**

a) Composition of the dissolution medium, pH, ionic strength, viscosity.

b) Type of dissolution equipment.

c) Temperature of the medium

d) Volume of dissolution medium

e) Intensity of agitation

f) Sink or non-sink conditions (under a sink condition, the concentration of the drug should not exceed 10 – 15% of its maximum solubility in the dissolution medium in use).

g) Sensitivity of analytical method used to determine drug concentration in the release medium

The rate and extent of dissolution of the drug from the capsule dosage form is tested by a dissolution test. This test provides means of quality control in ensuring that

1. Different batches of the drug product have similar drug release characteristics; and
2. That a given batch has similar dissolution as the batch of capsules that was shown initially to be clinically effective.

The same apparatus, dissolving medium, and test are used in the compendial dissolution test for capsules as they are for uncoated and plain-coated tablets. The contents of a certain number of capsules might be removed, and the empty capsule shells can be dissolved in the dissolving medium, prior to actually continuing with the sample and chemical analysis, if the capsule shells are causing an issue with the analysis (PA, 2023).

According to the Food and Drug Administration, the primary objective of developing and assessing an IVIVC is to establish the dissolution test as a substitute for human trials (FDA) (Suarez-Sharp *et al.*, 2016). Following modest formulation and manufacturing adjustments, analytical data from drug dissolution testing is frequently adequate to confirm the safety and efficacy of a medicinal product without *in vivo* experiments (Qureshi and Shabnam, 2001). As a result, precise and repeatable findings must be produced by dissolving testing carried out in the dissolution apparatus (WP, n.d.).

### 2.3. Pharmacokinetic Parameters (Mojaverian et al., 1997)

The pharmacokinetic parameters were obtained from the well authentic published literature and the values reported there are as follows:

Bioavailability, F = 6.5%

Volume of distribution, Vd = 65 l

Half-life ($t_{1/2}$) = 11 h

Elimination rate constant, ke = 0.693/half-life = 0.693/11 = 0.063 per h

### 2.4. Evaluation of Predictability of the Model

Percentage prediction error (% PE) for Cmax and AUC can be determined by the following formula:

$$\%\ Prediction\ Error = \frac{Predicted\ \ Parameter - Observed\ \ Parameter}{Predicted\ \ Parameter} \times 100$$

A value of ±20% or less confirms predictability of the model. A percentage prediction error of greater than +/- 20% is indicative of inadequate or lack of predictability (USFDA, 1997).

## 3. Results

### 3.1. Physical Appearance

The primary packaging of the reference product is done in Alu-Alu blister packing while the Test Product "A" is done in strip packing and Text Product "B" in Alu-Alu blister packing.

Dabigatran pellets are filled in with hard gelatin capsule.

### 3.2. Weight Variation Test

Since the percentage deviation of the net weight of each capsule for the Reference Product, Test Product A, and Test Product B lie within ± 7.5% from the average weight, all the products obey the required standard properties (Tables 3, 4 and 5).

### 3.3. Length and Diameter Test

The length and diameter for the Reference Product, Test Product A and Test Product B were measured in mm.

The percentage deviation of the length and diameter of the Reference product, Test Product A and Test Product B lies within ±1, uniform with the average length and diameter (Tables 6, 7 and 8).

**Table 3: Weight Variation Test of Reference Product (Pradaxa 110)**

| S. No. | Filled Weight | Empty Weight | Net Weight | % Deviation of Net Weight |
|---|---|---|---|---|
| 1 | 384 | 72 | 312 | -0.68438644 |
| 2 | 377 | 70 | 307 | -2.275982811 |
| 3 | 383 | 70 | 313 | -0.366067165 |
| 4 | 390 | 75 | 315 | 0.270571383 |
| 5 | 394 | 76 | 318 | 1.225529206 |
| 6 | 382 | 69 | 313 | -0.366067165 |
| 7 | 376 | 67 | 309 | -1.639344262 |
| 8 | 382 | 64 | 318 | 1.225529206 |
| 9 | 382 | 69 | 313 | -0.366067165 |
| 10 | 391 | 73 | 318 | 1.225529206 |
| 11 | 383 | 71 | 312 | -0.68438644 |
| 12 | 388 | 70 | 318 | 1.225529206 |
| 13 | 385 | 71 | 314 | -0.047747891 |
| 14 | 387 | 72 | 315 | 0.270571383 |
| 15 | 385 | 75 | 310 | -1.321024988 |
| 16 | 383 | 68 | 315 | 0.270571383 |
| 17 | 385 | 68 | 317 | 0.907209932 |
| 18 | 388 | 70 | 318 | 1.225529206 |
| 19 | 383 | 67 | 316 | 0.588890657 |
| 20 | 382 | 70 | 312 | -0.68438644 |
| **Average** | 384.5 | 70.35 | 314.15 | |

**Table 4: Weight Variation Test of Test Product A**

| S. No. | Filled Weight | Empty Weight | Net Weight | % Deviation of Net Weight |
|---|---|---|---|---|
| 1 | 430 | 96 | 334 | 3.888024883 |
| 2 | 418 | 96 | 322 | 0.155520995 |
| 3 | 412 | 98 | 314 | -2.33281493 |
| 4 | 403 | 96 | 307 | -4.510108865 |
| 5 | 423 | 97 | 326 | 1.399688958 |
| 6 | 437 | 97 | 340 | 5.754276827 |
| 7 | 410 | 91 | 319 | -0.777604977 |
| 8 | 417 | 91 | 326 | 1.399688958 |
| 9 | 413 | 93 | 320 | -0.466562986 |
| 10 | 412 | 95 | 317 | -1.399688958 |

**Table 4 (Cont.)**

| | | | | |
|---|---|---|---|---|
| 11 | 419 | 94 | 325 | 1.088646967 |
| 12 | 428 | 95 | 333 | 3.576982893 |
| 13 | 420 | 96 | 324 | 0.777604977 |
| 14 | 403 | 96 | 307 | -4.510108865 |
| 15 | 410 | 97 | 313 | -2.643856921 |
| 16 | 430 | 97 | 333 | 3.576982893 |
| 17 | 411 | 95 | 316 | -1.710730949 |
| 18 | 407 | 96 | 311 | -3.265940902 |
| 19 | 417 | 92 | 325 | 1.088646967 |
| 20 | 408 | 90 | 318 | -1.088646967 |
| **Average** | 416.4 | 94.9 | 321.5 | |

**Table 5: Weight Variation test of Test Product B**

| S. No. | Filled Weight | Empty Weight | Net Weight | Percentage Deviation |
|---|---|---|---|---|
| **1** | 395 | 78 | 317 | 1.197126895 |
| 2 | 371 | 74 | 297 | -5.18754988 |
| 3 | 397 | 72 | 325 | 3.750997606 |
| 4 | 391 | 78 | 313 | -0.07980846 |
| 5 | 387 | 74 | 313 | -0.07980846 |
| 6 | 389 | 73 | 316 | 0.877893057 |
| 7 | 399 | 73 | 326 | 4.070231445 |
| 8 | 397 | 75 | 322 | 2.793296089 |
| 9 | 389 | 73 | 316 | 0.877893057 |
| 10 | 385 | 73 | 312 | -0.399042298 |
| 11 | 390 | 74 | 316 | 0.877893057 |
| 12 | 385 | 77 | 308 | -1.675977654 |
| 13 | 390 | 75 | 315 | 0.558659218 |
| 14 | 390 | 73 | 317 | 1.197126895 |
| 15 | 386 | 74 | 312 | -0.399042298 |
| 16 | 375 | 71 | 304 | -2.952913009 |
| 17 | 388 | 77 | 311 | -0.718276137 |
| 18 | 382 | 74 | 308 | -1.675977654 |
| 19 | 381 | 76 | 305 | -2.63367917 |
| 20 | 388 | 76 | 312 | -0.399042298 |
| **Average** | 387.75 | 74.5 | 313.25 | |

**Table 6: Length and Diameter Test of the Reference Product**

| S. No. | Length | Diameter | % Deviation in Length | % Deviation in Diameter |
|---|---|---|---|---|
| 1 | 19.84 | 6.86 | 3.776545664 | 2.388059701 |
| 2 | 19.04 | 6.53 | -0.407992468 | -2.537313433 |
| 3 | 19.05 | 6.71 | -0.355685741 | 0.149253731 |
| 4 | 18.89 | 6.81 | -1.192593368 | 1.641791045 |
| 5 | 18.9 | 6.67 | -1.140286641 | -0.447761194 |
| 6 | 19.22 | 6.69 | 0.533528612 | -0.149253731 |
| 7 | 19.17 | 6.67 | 0.271994979 | -0.447761194 |
| 8 | 18.96 | 6.65 | -0.826446281 | -0.746268657 |
| 9 | 19.06 | 6.74 | -0.303379015 | 0.597014925 |
| 10 | 19.05 | 6.67 | -0.355685741 | -0.447761194 |
| **Average** | 19.118 | 6.7 | | |

**Table 7: Length and Diameter Test of the Test Product A**

| S. No. | Length | Diameter | % Deviation in Length | % Deviation in Diameter |
|---|---|---|---|---|
| 1 | 21.69 | 7.67 | 1.251050322 | 1.0673343 |
| 2 | 21.53 | 7.42 | 0.504154607 | -2.226907366 |
| 3 | 21.41 | 7.56 | -0.056017179 | -0.382132033 |
| 4 | 21.22 | 7.58 | -0.94295584 | -0.1185927 |
| 5 | 21.31 | 7.55 | -0.522827 | -0.5139017 |
| 6 | 21.27 | 7.51 | -0.709550929 | -1.040980366 |
| 7 | 21.59 | 7.64 | 0.7842405 | 0.6720253 |
| 8 | 21.3 | 7.74 | -0.569507982 | 1.989721966 |
| 9 | 21.34 | 7.69 | -0.382784054 | 1.330873633 |
| 10 | 21.56 | 7.53 | 0.644197554 | -0.777441033 |
| **Average** | 21.422 | 7.589 | | |

**Table 8: Length and Diameter Test of the Test Product B**

| S. No. | Length | Diameter | % Deviation in Length | % Deviation of Diameter |
|---|---|---|---|---|
| 1 | 19.08 | 6.7 | -0.15176095 | 0.052266109 |
| 2 | 19.11 | 6.68 | 0.005233136 | -0.246397372 |
| 3 | 19.11 | 6.71 | 0.005233136 | 0.20159785 |
| 4 | 19.16 | 6.72 | 0.266889947 | 0.35092959 |
| 5 | 19.06 | 6.7 | -0.256423675 | 0.052266109 |
| 6 | 19.02 | 6.71 | -0.465749123 | 0.20159785 |
| 7 | 19.05 | 6.73 | -0.308755037 | 0.500261331 |
| 8 | 19.02 | 6.71 | -0.465749123 | 0.20159785 |
| 9 | 19.09 | 6.66 | -0.099429588 | -0.545060853 |
| 10 | 19.09 | 6.73 | -0.099429588 | 0.500261331 |
| **Average** | 19.07 | 6.705 | | |

### 3.4. Disintegration Test

The average time taken for the Reference Product, Test Product A and Test Product B to disintegrate was 23.38 min, 24.02 min, and 25.35 min respectively (Table 9).

Since the samples were filled in hard gelatin capsules, the disintegration time for hard gelatin capsules should not exceed 30 min.

### 3.5. Dissolution Test

$$\%\ Drug\ Release = \frac{Weight\ of\ Standard * Dilution\ Factor * Potency * Volume * Area\ of\ Sample * 100}{Area\ of\ Standard * Label\ Claim}$$

$$Dilution\ Factor = \frac{1}{25} \times \frac{2}{20} \times \frac{Molecular\ Weight\ of\ Dabigatran\ Etexilate}{Molecular\ Weight\ of\ Dabigatran\ Etexilate\ Mesylate}$$

Amount Released = (% released * total amount of tablet)/100

Discrete amount released within sampling interval = Amount released at time ($t_2$) – Amount released at time ($t_1$).

Predicted total blood amount (mg) after absorption was calculated by adding all the predicted blood drug amounts for every time.

Predicted Concentration (ng/mL) at Times = Predicted Total Blood Amount (mg) after

Absorption * F*1000/Vd

The predicted and observed pharmacokinetic parameter for the tablet was listed in Table along with % prediction error.

**Table 9: Disintegration Time for the Reference Product, Test Product A and Test Product B**

| Disintegration Time | Reference Product | Test Product A | Test Product B |
|---|---|---|---|
| First Test | 23.24 | 24.25 | 25.32 |
| Second Test | 24.12 | 24.52 | 26.28 |
| Third Test | 22.09 | 25.37 | 24.46 |
| **Average** | 23.39 | 24.02 | 25.35 |

## 4. Discussion

The % prediction error within ± 20% indicates similarity of *in vivo* performance in comparison with reference products according to bioequivalence practice. The predicted and actual pharmacokinetic parameters were compared.

The observed value of Cmax and AUC of the Reference Product was 105.63 ng/mL and 1708.28 ng*h/mL respectively. Similarly, Cmax AUC and the %prediction error of "Product A" from the convolution method was found to be 105.08 ng/mL, 1722.91 ng*h/mL while the Cmax and AUC of "Product B" was found to be 96.83 ng/mL, and 1583.4 ngh/mL. The percentage prediction error (%PE) values for Cmax and AUC were found to be 0.54% and -0.85% for "Product A" and 9.09% and 7.89% for "Product B" respectively. The predicted error of AUC and Cmax are within the ±20% range for both local generic products (Product A and Product B) (Tables 10 and 11).

The findings suggested that prospective approaches should be used to create IVIVC and forecast *in vivo* pharmacokinetic profiles for bioequivalence studies for generic product development.

As a result of these findings, it is obvious that in order to assess the influence of formulation and/or manufacturing modifications on the product's plasma drug levels, dissolving properties of the test and reference products should be assessed, and their corresponding blood levels determined (Figures 4, 5 and 6).

**Table 10: Predicted Value, Observed Value and % Prediction Error of Cmax and AUC of Dabigatran Capsule for Test Product A**

| S. No. | Parameters | Predicted Value (Reference Product) | Observed Value | % Prediction Error |
|---|---|---|---|---|
| 1 | Cmax (ng/mL) | 105.63 | 105.08 | 0.52% |
| 2 | AUC (ng.hr/mL) | 1708.28 | 1722.91 | -0.85% |

**Note:** The percentage prediction error for AUC was found to be within +/- 20%.

**Table 11: Predicted Value, Observed Value and % Prediction Error of Cmax and AUC of Dabigatran Capsule for Test Product B**

| S. No. | Parameters | Predicted Value (Reference Product) | Observed Value | % Prediction Error |
|---|---|---|---|---|
| 1 | Cmax (ng/mL) | 105.63 | 96.83 | 9.09% |
| 2 | AUC (ng.h/mL) | 1708.28 | 1583.4 | 7.89% |

**Note:** The percentage prediction error for AUC was found to be within +/- 20%.

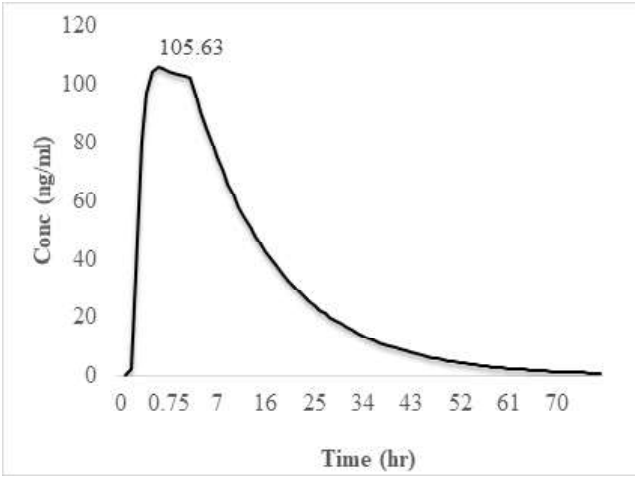


**Figure 4: Plasma Drug Concentration Time Profiles of Reference Drug Derived from *In Vitro* Dissolution Profiles**

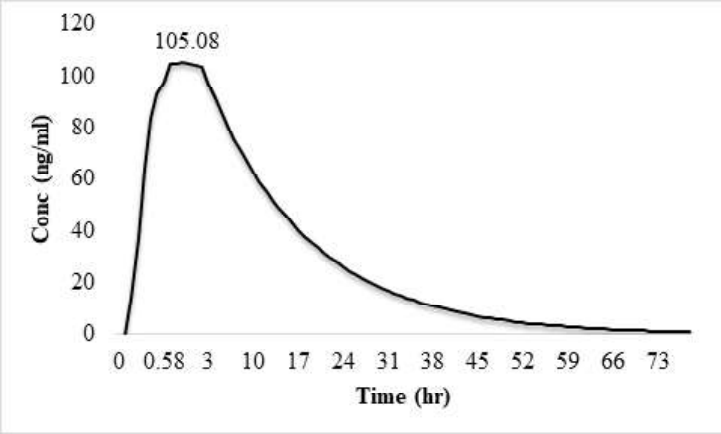


**Figure 5: Plasma Drug Concentration Time Profiles of Test Product A Derived from *In Vitro* Dissolution Profiles**

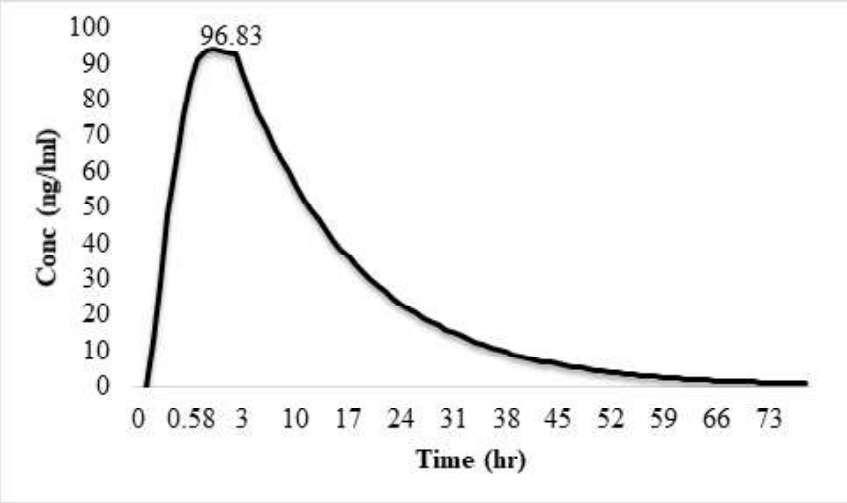


**Figure 6: Plasma Drug Concentration Time Profiles of Test Product B Derived from *In Vitro* Dissolution Profiles**

Furthermore, if one wishes to optimize their formulation, the convolution technique aids in the prediction of blood levels of test formulations from *in vitro* data, and only the formulations with mathematically predicted blood levels equivalent to their reference product will be chosen and incorporated for animal studies. As a result, the convolution approach aids in the reduction of quantity/number utilized in in vivo pharmacokinetic research, resulting in a lower final manufacturing cost.

## 5. Conclusion

The percentage prediction error for AUC and Cmax calculated were within ± 20%. The findings suggested that the test samples (Dabigatran capsules) are bioequivalent to the reference product for dissolution method.

From this, we can conclude that the rate and extent of absorption of test products were found to be similar in convolution method.

## Conflicts of Interest

Authors declares that there is no conflict of interest related to this.

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## List of Abbreviations

| | | |
|---|---|---|
| AUC | : | Area Under the Curve |
| $C_{max}$ | : | Maximum plasma drug concentration |
| CDR | : | Cumulative Drug Release |
| NLT | : | Not Less Than |
| $T_{max}$ | : | Time at which maximum plasma drug concentration was attained |
| IVIVC | : | *In Vitro In Vivo* Correlation |

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